UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,905	03/23/2004	David Scheinberg	D6499	2406

7590 08/29/2008

Benjamin Aaron Adler
ADLER & ASSOCIATES
8011 Candle Lane
Houston, TX 77071

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
08/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 7/22/2008 in response to the previous Final Office Action (4/04/2008) is acknowledged, but has not been entered. The amendment has not been entered because it contains claim limitation which were not previously searched or considered. For example, Claim 1 has been amended to include the limitation of "administering a pharmacologically effective dose of one or more diuretic". As such, the limitation of "one or more diuretic" broadens the scope of the previous claim which recited administration of "a diuretic", e.g., one diuretic. In the instant case, the Examiner acknowledges and does not dispute Applicants submission (page 6 of Remarks) that Claim 1, as originally filed, recited "administering a pharmacologically effective dose of at least one adjuvant..." which adjuvant was limited to competitive metal blockers, chelators and diuretics in dependent claims. However, the terminology of claim 1, as originally filed, does not appear to indicate that one or more diuretics may be administered, but appears to reasonably convey that the a combination of diuretic, e.g., singular, competitive metal blocker, or chelator may be administered.

Claims 1-2, 4-5, 8-12, 32, 49, 51-53 and 58-61 are currently pending and under consideration.

Rejections Maintained:

The following rejections are maintained in view of Applicants arguments which appear to be solely drawn to the currently amended claims that have not been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-5, 8, 10-11, 32, 49, 51-53 and 59-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennel et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15: 235-244, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731), Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113, *of record*), and Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60, *of record*) in further view of Nair et al. (J. Radiat. Res. 2001; 42: 21-37).

Kennel et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate (abstract). The reference further teaches that while the isotope coupled to the targeting monoclonal antibody delivers a tumorcidal dose to the lung, the radiotoxicity associated with decay daughter isotopes released from the target organ limit the effectiveness of the therapy (page 242, 2nd column, last paragraph). For example, Kennel et al. teach at necropsy, animals had total ablation of bone marrow cells, splenic atrophy, some damage to the lining of their stomachs and intestine and excess accumulation of undigested food in their stomachs (page 240, 1st column, paragraph bridging page 239).

Kennel et al. do not explicitly teach administering a competitive metal blocker such as bismuth subnitrate, a chelator such as DMPS or a diuretic such as furosemide in combination with the ^{225}Ac conjugate.

Satoh et al. teach the effects of preinduction of metallotheionein (MT) by bismuth subnitrate (BSN) on the adverse effects and antitumor activity of γ–ray irradiation in mice (abstract). In particular, the reference teaches that oral administration of BSN markedly reduced the lethal effects and bone marrow damage by γ–ray irradiation without compromising the tumor-reducing effect (page 1730, 1st column, last paragraph). As such, Satoh et al. teach that bismuth subnitrate pretreatment is an effective method for protection against side-effects in radiotherapy (abstract).

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As

a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Nair et al. teach radioprotector in radiotherapy. In particular, the reference teaches that while acute toxicity has been a main reason for radioprotectors failure in clinical applications, the use of nontoxic amounts of several radioprotectors having a different mechanism of action can overcome the problems associated with their toxicity.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention to combine the teachings of the references so as to modify the method taught by Kennel et al. to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al.. One would have been motivated to do so because each of the references teach that the agents are effective at reducing toxicities associated with radiotherapies. Moreover, as taught by Nair et al., combining several radioprotectors having a different mechanism of action can overcome problems associated with radioprotector toxicity. Thus, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by Kennel et al. to include

administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al., one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney, as well as bone marrow damage.

Claims 1-2, 4-5, 8-12, 32, 49, 51-53 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheinberg et al. (US 2002/0058007, 2002, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731), Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113, *of record*), and Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60, *of record*) and in further view of Nair et al. (J. Radiat. Res. 2001; 42: 21-37).

Scheinberg et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 2, paragraph 0016). With regards to the cancer, the publication teaches (page 4, paragraph 0037) that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regards to the ^{225}Ac conjugate, the publication teaches (page 2, paragraph 0017) that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. For example, Scheinberg et al. provides (page 2, paragraph 0021) an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Moreover, the publication discloses the toxicity of ^{225}Ac constructs, wherein histological analysis of deceased mice showed gastrointestinal mucosal sloughing and bond marrow hyplasia, consistent with severe radiotoxicity (column 8, paragraph 0097).

Scheinberg et al. does not explicitly teach administering a competitive metal blocker such as bismuth subnitrate, a chelator such as DMPS or a diuretic such as furosemide in combination with the ^{225}Ac conjugate.

Satoh et al. teach the effects of preinduction of metallotheionein (MT) by bismuth subnitrate (BSN) on the adverse effects and antitumor activity of γ–ray irradiation in mice (abstract). In particular, the reference teaches that oral administration of BSN markedly reduced the lethal effects and bone marrow damage by γ–ray irradiation without compromising the tumor-reducing effect (page 1730, 1st column, last paragraph). As such, Satoh et al. teach that bismuth subnitrate

pretreatment is an effective method for protection against side-effects in radiotherapy (abstract).

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Nair et al. teach radioprotector in radiotherapy. In particular, the reference teaches that while acute toxicity has been a main reason for radioprotectors failure in clinical applications, the use of nontoxic amounts of several radioprotectors having a different mechanism of action can overcome the problems associated with their toxicity.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention to combine the teachings of the references so as to modify the method taught by Kennel et al. to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al.. One would have been motivated to do so because each of the references teach that the agents are effective at reducing toxicities associated with radiotherapies. Moreover, as taught by Nair et al., combining several radioprotectors having a

different mechanism of action can overcome problems associated with radioprotector toxicity. Thus, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by Kennel et al. to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al., one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney, as well as bone marrow damage.

Claims 1-2, 4-5, 8-12, 32, 49, 51-53 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDevitt et al. (Science 2001; 294: 1537-1540, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731), Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113, *of record*), and Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60, *of record*) and in further view of Nair et al. (J. Radiat. Res. 2001; 42: 21-37).

McDevitt et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 1537, Abstract). With regards to the cancer, the reference teaches (page 1537, Abstract) that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regards to the ^{225}Ac conjugate, the reference teaches (page 1538, 1st column, 2nd full paragraph) that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. For example, Scheinberg et al. provides (page 1538, 1st column, 2nd full paragraph) an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Moreover, the publication discloses the biodistribution of ^{225}Ac conjugates in tumor bearing mice, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi, e.g. *daughter of ^{225}Ac*, accumulation in the kidney as a result of decay of the

daughters from nontargeted constructs (page 1538, Figure 1B).

McDevitt et al. does not explicitly teach administering a diuretic such as furosemide, a dithiol chelate and a metal blocker such as bismuth subnitrate in combination with the ^{225}Ac conjugate.

Satoh et al. teach the effects of preinduction of metallotheionein (MT) by bismuth subnitrate (BSN) on the adverse effects and antitumor activity of □ □ ray irradiation in mice (abstract). In particular, the reference teaches that oral administration of BSN markedly reduced the lethal effects and bone marrow damage by γ–ray irradiation without compromising the tumor-reducing effect (page 1730, 1st column, last paragraph). As such, Satoh et al. teach that bismuth subnitrate pretreatment is an effective method for protection against side-effects in radiotherapy (abstract).

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Nair et al. teach radioprotector in radiotherapy. In particular, the reference teaches that while acute toxicity has been a main reason for radioprotectors failure in clinical applications, the use of nontoxic amounts of several radioprotectors having a different mechanism of action can

overcome the problems associated with their toxicity.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention to combine the teachings of the references so as to modify the method taught by McDevitt to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al.. One would have been motivated to do so because each of the references teach that the agents are effective at reducing toxicities associated with radiotherapies. Moreover, as taught by Nair et al., combining several radioprotectors having a different mechanism of action can overcome problems associated with radioprotector toxicity. Thus, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by McDevitt to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al., one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney, as well as bone marrow damage.

Therefore, No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf
Examiner
Art Unit 1642

/Brandon J Fetterolf/
Examiner, Art Unit 1642